FORM PTO-1390 (REV 5-93)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY DOCKET NO. 108172-00071
	TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	DATE: June 7, 2001
		U.S. APPLN. NO. (IF KNOWN, SEE 37 C.F.R. 1.5) 09/856470

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US99/27919	December 8, 1999	December 8, 1998

TITLE OF INVENTION: GENETIC MARKERS WHICH IDENTIFY INDIVIDUALS WHO IMPROVE THEIR CHOLESTEROL LEVELS AND DIABETES STATUS WITH EXERCISE

APPLICANT(S) FOR DO/EO/US: James M. HAGBERG; Robert E. FERRELL; Alan SHULDINER

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
(THE BASIC FILING FEE IS ATTACHED)

2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. ☒ This express request to begin national examination procedures [35 U.S.C. 371(f)] at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. ☒ A proper demand for International Preliminary Amendment was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of the International Application as filed [35 U.S.C. 371(c)(2)]
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).

6. ☐ A translation of the International Application into English [35 U.S.C. 371(c)(2)].

7. ☒ Amendments to the claims of the International Application under PCT Article 19 [35 U.S.C. 371(c)(3)]
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 [35 U.S.C. 371(c)(3)].

9. ☐ An oath or declaration of the inventor(s) [35 U.S.C. 371(c)(4)].

10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 [35 U.S.C. 371(c)(5)].

Items 11 - 16 below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☒ Other items or information: Copies of: PCT/IPEA/402; PCT/IPEA/416; PCT/IB/306; Request for Change under PCT Rule 92bis; Response to Invitation to Correct Defects in the Demand; Demand for International Preliminary Examination; Demand; PCT/IB/308; PCT/IB/318; PCT/IB/304; Response to Invitation to Correct Defects; Response to Invitation to Correct Priority Claim; PCT/IB/316; Response to Invitation to Correct Defects; PCT/IB/304; published International Application No. PCT/US99/27919

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U.S. APPLN. NO. (IF KNOWN SEE 37 C.F.R. 1.5) 09/856470	INTERNATIONAL APPLICATION NO. PCT/US99/27919	ATTORNEY DOCKET NO. 108172-00071 DATE: June 7, 2001

17. ☒ The following fees are submitted:

Basic National Fee [37 C.F.R. 1.492(a)(1)-(5)]:

Search Report has been prepared by the EPO or JPO.....$860.00
International preliminary examination fee paid to USPTO (37 C.F.R. 1.482).....$690.00
No international preliminary examination fee paid to USPTO (37 C.F.R. 1.482) but international search fee paid to USPTO [37 C.F.R. 1.445(a)(2)].....$710.00
Neither international preliminary examination fee (37 C.F.R. 1.482) or international search fee [37 C.F.R. 1.445(a)(2)] paid to USPTO.....$1,000.00
International preliminary examination fee paid to USPTO (37 C.F.R. 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....$ 100.00

	CALCULATIONS	PTO USE ONLY
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 690.00	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date [37 C.F.R. 1.492(e)].	$	

Claims	Number Filed	Number Extra	Rate		
Total Claims	5 - 20 =	0	X $ 18.00	$ 0	
Independent Claims	5 - 3 =	2	X $ 80.00	$ 160	
Multiple dependent claim(s) (if applicable)			+ $270 00	$ 0	
TOTAL OF ABOVE CALCULATIONS =				$ 850	
Reduction by one-half for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 C.F.R. 1.9, 1.27, 1.28). -				$	
SUBTOTAL =				$ 850	
Processing fee of $130.00 for furnishing the English translation later the ☐ 20 ☐ 30 months from the earliest claimed priority date [37 C.F.R. 1.492(f)]. +				$	
TOTAL NATIONAL FEE =				$ 850	
Fee for recording the enclosed assignment [37 C.F.R. 1.21(h)]. The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. 3.28, 3.31). $40.00 per property +				$	
TOTAL FEES ENCLOSED =				$ 850	
				Amount to be refunded	$
				Charged	$

a. ☒ A check in the amount of $850 to cover the above fees is enclosed.
b. ☐ Please charge my Deposit Account No. 01-2300 in the amount of $ to cover the above fee. A duplicate copy of this sheet is enclosed.
c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 01-2300.

NOTE: Where an appropriate time limit under 37 C.F.R. 1.494 or 1.495 has not been met, a petition to revive [37 C.F.R. 1.137(a) or (b)] must be filed and granted to restore the application to pending status.

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Richard J. Berman
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#27467v1<TECH>

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

HAGBERG, et al. Attorney Dkt. No.: 108172-00071

Appln. No.: New application based on PCT/US99/27919

Filed: Concurrently herewith

For: GENETIC MARKERS WHICH IDENTIFY INDIVIDUALS WHO IMPROVE THEIR CHOLESTEROL LEVELS AND DIABETES STATUS WITH EXERCISE

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231 June 7, 2001

Sir:

Please amend the above-identified application as follows:

IN THE SPECIFICATION:

Before line 1, page 1 insert

--CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a National Stage entry of International Application No. PCT/US99/27919, filed December 8, 1999, which claims priority from provisional application No. 60/111,494, filed December 8, 1998, and provisional application No. 60/112,604, filed December 17, 1998, the entire specification, claims and drawings of which are incorporated herewith by reference. --

REMARKS

In the event that any fees are due with respect to the filing of this paper, please charge our deposit account No. 01-2300.

Respectfully submitted,

Richard J. Berman
Registration No. 39,107

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#27471v1 <TECH>

GENETIC MARKERS WHICH IDENTIFY INDIVIDUALS WHO IMPROVE THEIR CHOLESTEROL LEVELS AND DIABETES STATUS WITH EXERCISE

FIELD OF THE INVENTION

The present invention relates to identifying one or more genetic markers which correlate with greater success in improving cholesterol levels and diabetes status in individuals with and without high cholesterol levels or diabetes.

BACKGROUND OF THE INVENTION

Studies have shown that individuals suffering from or at risk of developing high cholesterol levels or diabetes can alleviate symptoms or otherwise improve their conditions through exercise. Unfortunately, some individuals, no matter how rigorously they exercise, are unable to improve their conditions, while others benefit to a much greater extent than predicted. These results underscore the fact that many factors contribute to an individual's well-being. Such factors include, for example, behaviors such as diet and exercise, genetic makeup, and environment. While behavior and environment can be controlled, altered or regulated, an individual's genetic makeup is essentially predetermined and set at birth. The present inventors hypothesized that upon identifying the genetic makeup of a population suffering from or at risk of developing high cholesterol levels or diabetes and observing that some individuals of the population improve their cholesterol levels and diabetic status from a change of behavior to a much greater or lesser extent than expected, a correlation could be made between the presence or absence of certain genetic markers and success in improving cholesterol levels and diabetic status.

An object of the present invention is to identify one or more genetic markers which positively correlate with greater success in improving cholesterol levels and diabetes status in individuals with and without high cholesterol levels or diabetes.

SUMMARY OF THE INVENTION

The present inventors have discovered a number of genetic markers which positively correlate with greater success in improving cholesterol levels and diabetes status in diabetic, hypercholesteremic or at risk individuals, as compared with other genetic makeup at the same gene loci. Therefore, a first embodiment of the present invention is directed to a method of improving cholesterol levels in a subject with increased cholesterol levels or at risk of developing such a condition, the method comprising:

identifying a subject with hypercholesteremia or at risk of developing such a condition having an allele and/or a genotype at a gene locus which positively correlates with greater success in improving cholesterol levels in hypercholesteremic individuals, as compared with other alleles and/or genotypes at the same gene locus; and

engaging the subject in exercise training for a period of time sufficient to improve the cholesterol levels in the subject.

A second embodiment of the present invention is directed to a method of improving diabetes status in a subject with diabetes or at risk of developing diabetes, the method comprising:

identifying a subject with diabetes or at risk of developing diabetes having an allele and/or a genotype at a gene locus which positively correlates with greater success in improving diabetes status in diabetic individuals, as compared with other alleles and/or genotypes at the same gene locus; and

engaging the subject in exercise training for a period of time sufficient to improve the diabetes status in the subject.

DETAILED DESCRIPTION OF THE INVENTION

The inventors have found that a number of genetic markers positively correlate with greater success in improving cholesterol levels or diabetes status in individuals with hypercholesteremia or diabetes, or at risk of developing such disorders, as compared with other genetic makeup at the same gene loci.

Markers which the inventors have investigated include the glucose transport 4 (GLUT4) gene, the myostatin gene and the insulin receptor substrate-1 (IRS-1) gene.

The term "improved cholesterol levels" means an improvement in at least one characteristic area which is associated with hypercholesteremia. An improvement may be in one or more of the following characteristic areas (this list is non-exhaustive and includes overlapping and representative examples only): change in cholesterol metabolism, increase in high density lipoprotein cholesterol (HDL-C) levels, increase in high density lipoprotein cholesterol 2 (HDL_2-C) levels, decrease in low density lipoprotein cholesterol (LDL-C) levels or increase in the ratio of HDL-C or HDL_2-C levels as compared to LDL-C levels. These improvements may be measured by, for example, plasma cholesterol tests conducted before and after exercise training. An improvement in cholesterol levels in accordance with the invention may be found both in individuals with hypercholesteremia and in individuals at risk of developing such a disorder.

The term "improved diabetes status" means an improvement in at least one characteristic area which is associated with diabetes. An improvement may be in one or more of the following characteristic areas (this list is non-exhaustive and includes overlapping and representative examples only): change in glucose metabolism, change in insulin metabolism, change in glucose levels from a baseline determination, change in insulin levels from a baseline determination, change in fasting plasma glucose levels, change in fasting plasma insulin levels or change in acute insulin response to glucose. These improvements may be measured by, for example, glucose tolerance tests conducted before and after exercise training. An improvement in diabetes status in accordance with the invention may be found both in individuals with diabetes and in individuals at risk of developing diabetes.

The term "single course of exercise", as used throughout this application, means a cardiovascular exercise session of any type which is conducted during

one day. An exercise session may comprise an aerobics class, treadmill training, step machine, or any other suitable cardiovascular exercise regimen. For most cases, exercise may be completed in, for example, 30 minutes to 3 hours, with optional brief rest periods of 3-15 minutes, however this amount would vary depending on the health and endurance of the subject.

The term "extensive exercise" means about 10 single courses of exercise or more, preferably at least 15, at least 20, or at least 25 single courses of exercise, over a defined period of time ("the exercise period"). The exercise period in the case of an extensive exercise protocol may be from about 50-400 days, preferably from about 70-350 days or 100-300 days.

The time between exercise courses depends on the health and endurance of the subject. Preferably, the time between exercise courses may be from about 1-3 days or more.

The present inventors have discovered that hypercholesteremic or diabetic individuals or those at risk of developing hypercholesteremia or diabetes with different genotypes for genes which control the manufacture of certain proteins exhibit different degrees of success in improving their cholesterol levels and diabetes status through exercise. The inventors have surprisingly discovered that each genotype potentially can benefit from exercise, however, the amount of exercise which produces the most benefits varies according to genotype. These results could not have been predicted from initial patient screening.

Glucose transport in skeletal muscle is mainly facilitated by the insulin-responsive GLUT4. In the basal state, GLUT4 is stored in a transporter-enriched intracellular pool. Following insulin stimulation, GLUT4 is translocated from the intracellular compartment to both the plasma membrane and the T-tubules.

The inventors have found that subjects having a BamHI "AA" genotype for a GLUT4 gene exhibit a greater improvement in cholesterol levels than those with a "GG" or "AG" genotype, after extensive exercise.

Therefore, one method of improving cholesterol levels in a subject in need of such improvement according to the invention comprises identifying a subject having a BamHI "AA" genotype for a GLUT4 gene, wherein the subject is in need of improved cholesterol levels and engaging the subject in extensive exercise training for a period of time sufficient to improve the cholesterol levels in the subject.

Myostatin, also known as growth/differentiation factor-8 (Gdf8), is a member of the transforming growth factor-beta (TGF-β) superfamily, which encompasses a large number of growth and differentiation factors that play important roles in regulating embryonic development and in maintaining tissue homeostasis in adult animals. During early stages of embryogenesis, myostatin expression is restricted to the myotome compartment of developing somites. At later stages and in adult animals, myostatin is expressed in many different muscles throughout the body.

The inventors have found that subjects having a "12" genotype for exon 2 of the myostatin gene exhibit a greater improvement in cholesterol levels than those with a "11" genotype, after extensive exercise.

Therefore, another method of improving cholesterol levels in a subject in need of such improvement according to the invention comprises identifying a subject having a "12" genotype for exon 2 of a myostatin gene, wherein the subject is in need of improved cholesterol levels and engaging the subject in extensive exercise training for a period of time sufficient to improve the cholesterol levels in the subject.

The inventors have also found that diabetics or those at risk of developing diabetes having a "11" genotype at exon 2 of the myostatin gene improve their diabetes status more with extensive exercise training than those having a "12" genotype.

Therefore, a method of improving diabetes status in a subject in need of such improvement comprises identifying a subject having a "11" genotype for exon 2 of a myostatin gene, wherein the subject is in need of improved diabetes

status and engaging the subject in extensive exercise training for a period of time sufficient to improve the diabetes status in the subject.

IRS-1 is a 185 kDa protein which is activated rapidly upon insulin stimulation of cells, and is a key mediator of an insulin-regulated biological activity. The amino-terminal region of the protein contains interaction modules that facilitate its binding to receptors of insulin. The remainder of the molecule contains numerous tyrosine containing motifs, which, when phosphorylated by the insulin receptor tyrosine kinase, serve as binding regions for a variety of cellular proteins containing a so-called "SH2" domain.

The inventors have found that subjects having a "12" genotype for the IRS-1 gene exhibit a greater improvement in cholesterol levels than those with a "11" genotype, after extensive exercise.

Therefore, in accordance with this aspect of the present invention, a method of improving cholesterol levels in a subject in need of such improvement comprises identifying a subject having a "12" genotype for an IRS-1 gene, wherein the subject is in need of improved cholesterol levels and engaging the subject in extensive exercise training for a period of time sufficient to improve the cholesterol levels in the subject.

EXAMPLES

Example 1. Variations in Improvement of Cholesterol Levels in Subjects with Different GLUT4 BamHI, Myostatin and IRS-1 Genotypes After Extensive Exercise

DNA was obtained from obese sedentary men 50-65 yrs of age, and processed as follows.

Detection of (C581T) and (A30G) Substitution in GLUT4

Genotyping for the (C581T) and (A30G) substitutions in GLUT4 was performed by amplification using sense primer 5'-CAGTGCCCGGAGCAGGGAGGCGCT-3' and antisense primer 5'-

GCGAAGATGAAAGAACCGATCCTG-3' followed by digestion with the restriction endonucleases AvaII and BamHI, respectively. The presence of a C at np-518 yields major AvaII restriction fragments of 408 and 378 base pairs and the presence of a T at np-518 yields fragments of 119, 289 and 378 base pairs. The presence of an A at np-30 yields major BamHI fragments of 389 and 342 base pairs, while the presence of a G at np-30 yields fragments of 445 and 389 base pairs. All denotations of sequence positions are based on those recited in Bjorbaek et al. (1994), *Diabetes*, 43:976-983, hereby incorporated by reference.

Detection of Lys153Arg Substitution in Myostatin Exon 2

DNA amplification primers for exon 2 of the human myostatin gene were designed based on the cDNA sequence of human myostatin (GenBank Accession No. AF019627) and the genomic organization of the bovine myostatin gene (Grobert et al. (1998), *Mamm. Gen.* 9:210-213, incorportated by reference). Amplimers were sequenced directly using the dRhodamine ready reaction kit (Perkin Elmer) and analyzed on the ABI Prism Model 377 (Applied Biosystems) fluorescent sequencer. Sequences were aligned for comparison using SEQUENCHER™ 3.0 (Gene Codes). Primer 1 had the sequence 5'-GAAAACCCAAATGTTGCTTC-3', and primer 2 had the sequence 5'-TGTCTAGCTTATGAGCTTAGGG-3'. The temperature was 54°C, and the buffer was 2.0 mM MgCl. PCR products were digested with BanII and the digested products were run on 2% agarose gels.

Detection of Gly972Arg Substitution in IRS-1

A 220 bp region encompassing the Gly972Arg substitution was amplified from approximately 20 ng of genomic DNA with upstream primer 5'-GCAGCCTGGCAGGAGAGCCAT-3' and downstream primer 5'-CTCACCTCCTCTGCAGCAATG-3'. PCR products were digested with BstNI. The digested products were run on a 4% agarose gel, stained with

ethidium bromide, and visualized by UV transillumination. The expected digestion product sizes were 220 bp for Gly972 homozygotes, 164 bp and 56 bp for Arg972 homozygotes and 220 bp, 164 bp and 56 bp for heterozygotes.

Results

The subjects underwent 9 months of endurance exercise training to quantify, among other things, their improvements in plasma cholesterol levels. Subjects were initially stabilized on an American Heart Association low-fat diet and had fasting blood samples drawn for plasma cholesterol measurements. This diet was maintained throughout the 9 months of exercise training and subjects repeated the blood sampling for cholesterol levels after training. The data in Table 1 represent the change in HDL-C and HDL_2-C levels that occurred with exercise training. Subjects with the GLUT4 BamHI "AA" genotype increased their plasma HDL-C and HDL_2-C levels with exercise training substantially more than subjects with the GLUT4 BamHI "GG" or "AG" genotype. Furthermore, subjects with the myostatin exon 2 "12" genotype increased their plasma HDL-C and HDL_2-C levels with exercise training substantially more than subjects with the myostatin exon 2 "11" genotype. Lastly, subjects with the IRS-1 "12" genotype increased their plasma HDL-C and HDL_2-C levels with exercise training substantially more than subjects with the IRS-1 "11" genotype. Thus, these results indicate that GLUT4, myostatin exon 2 and IRS-1 genotypes identify those individuals most likely to improve their cholesterol levels with exercise training.

Table 1: Change with Exercise Training in Plasma Lipoprotein Levels as a Function of Genotype

	Change with Exercise Training	
GLUT4 BamHI	**HDL-C**	**HDL_2-C**

GG and AG genotype (n=13)	1.9 ± 3.8	0.7 ± 4.0
AA genotype (n=2)	16.9 ± 12.9	11.1 ± 15.0
Myostatin Exon 2		
11 genotype (n=13)	2.0 ± 4.0	0.4 ± 4.0
12 genotype (n=2)	15.8 ± 14.4	13.6 ± 11.5
IRS-1		
11 genotype (n=10)	2.9 ± 1.4	-0.1 ± 1.5
12 genotype (n=3)	11.4 ± 7.3	8.5 ± 6.6

Values are mean ± SD. Values are expressed as the change with 9 months of exercise training in HDL-C and HDL_2-C levels. Thus, positive values indicate a response that is greater after training.

Example 2. Variations in Improvement of Diabetes Status in Subjects with Different Myostatin Exon 2 Genotypes After Extensive Exercise

The subjects, detection of polymorphisms and the exercise regimen for these subjects was described in Example 1. Subjects underwent an oral glucose tolerance test with blood samples drawn for up to 3 hours after the ingestion of a standard glucose load. Subjects repeated the glucose tolerance test after training. The data in the following Table 2 represent the change in the integrated glucose area above baseline that occurred with the exercise training. Subjects with the myostatin exon 2 "11" genotype decreased their glucose areas more with exercise training than subjects with the myostatin exon 2 "12" genotype. These results indicate that myostatin exon 2 genotypes identify those individuals most likely to improve their diabetes status with exercise training.

Table 2: Change with Exercise Training in Integrated Glucose Area in Response to an Oral Glucose Tolerance Test as a Function of Genotype

Myostatin Exon 2 Genotype	Change with Exercise Training in Glucose Area
11 genotype (n=14)	-1941 ± 1260
12 genotype (n=3)	1180 ± 1641

Values are mean ± SD. Values are expressed as the change with 9 months of exercise training in integrated glucose area above baseline for 3 hours following a standard oral glucose challenge. Negative values indicate a response that is reduced after exercise training and positive values a response that is greater after training.

We claim:

1. A method of improving cholesterol levels in a subject in need of such improvement, the method comprising:

identifying a subject with hypercholesteremia or at risk of developing hypercholesteremia having a BamHI "AA" genotype for a glucose transport 4 gene, wherein the subject is in need of improved cholesterol levels; and

engaging the subject in extensive exercise training for a period of time sufficient to improve the cholesterol levels in the subject.

2. A method of improving cholesterol levels in a subject in need of such improvement, the method comprising:

identifying a subject with hypercholesteremia or at risk of developing hypercholesteremia having a "12" genotype for a myostatin exon 2 gene, wherein the subject is in need of improved cholesterol levels; and

engaging the subject in extensive exercise training for a period of time sufficient to improve the cholesterol levels in the subject.

3. A method of improving cholesterol levels in a subject in need of such improvement, the method comprising:

identifying a subject with hypercholesteremia or at risk of developing hypercholesteremia having a "12" genotype for an insulin receptor substrate-1 gene, wherein the subject is in need of improved cholesterol levels; and

engaging the subject in extensive exercise training for a period of time sufficient to improve the cholesterol levels in the subject.

4. A method of improving diabetes status in a subject in need of such improvement, the method comprising:

identifying a subject with diabetes or at risk of developing diabetes having a "11" genotype for a myostatin exon 2 gene, wherein the subject is in need of improved diabetes status; and

engaging the subject in extensive exercise training for a period of time sufficient to improve the diabetes status in the subject.

Docket No. 108172-00071 ARENT FOX KINTNER PLOTKIN & KAHN, PLLC

Declaration For U.S. Patent Application

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention **entitled**
(Insert Title) GENETIC MARKERS WHICH IDENTIFY INDIVIDUALS WHO IMPROVE THEIR CHOLESTEROL LEVELS AND DIABETES STATUS WITH EXERCISE
the specification of which is attached hereto unless the following box is checked:

☒ was filed on December 8, 1999 As PCT International Application
Number PCT/US99/27919 and was amended on _____
and/or was filed on June 7, 2001 As U.S. Patent Application
Number 09/856,470 and was amended on _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment referred to above.
I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56.
I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate or PCT International Application having a filing date before that of the application(s) for which priority is claimed:

(List prior foreign applications)	(Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed
				☐ Yes ☐ No
				☐ Yes ☐ No
				☐ Yes ☐ No

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

60/111,494 (Application Number)	December 8, 1998 (Filing Date)
60/112,604 (Application Number)	December 17, 1998 (Filing Date)

☐ See attached list for additional prior foreign or provisional applications.

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) or §365(c) of any PCT International application(s) designating the United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) (U.S. or PCT) in the manner provided by the first paragraph of 35, U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(List prior U.S. Applications or PCT International applications designating the U S)	(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
	(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

And I hereby appoint the firm of Arent Fox, Customer Number 004372 including as principal attorneys: Robert B. Murray, Reg. No. 22,980; Charles M. Marmelstein, Reg. No. 25,895; George E. Oram, Jr., Reg. No. 27,931; Douglas H. Goldhush, Reg. No. 33,125; David T. Nikaido, Reg. No. 22,663; Richard J. Berman, Reg. No. 39,107; King L. Wong, Reg. No. 37,500; James A. Poulos, III, Reg. No. 31,714; Murat Ozgu, Reg. No. 44,275; Robert K. Carpenter, Reg. No. 34,794; Gregory B. Kang, Reg. No. 45,273; Rustan Hill, Reg. No. 37,351; Carl Schaukowitch, Reg. No. 29,211; Kevin Turner, Reg. No. 43,437; Rhonda C. Barton, Reg. No. P47,271; Hans J. Crosby, Reg. No. 44,634, David D. Dzara, Reg. No. 47,543, Lynne D. Anderson, Reg. No. 46,412; David D. Dzara, Reg. No. 47,543; and Laurence J. Edson, Reg. No. 44,666.

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The undersigned hereby authorizes the U.S. attorneys named herein to accept and follow instructions from the undersigned's assignee, if any, and/or, if the undersigned is not a resident of the United States, the undersigned's domestic attorney, patent attorney or patent agent, as to any action to be take in the Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and the undersigned. In the event of a change in the person(s) from whom instructions may be taken, the U.S. attorneys named herein will be so notified by the undersigned

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

Full name of sole or first inventor James M. HAGBERG
Inventor's signature [signature] 4/15/01
Date
Residence 10941 Hilltop Lane, Columbia, MD 21044 MD
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Post Office Address Same as above

Full name of sole or second inventor Robert E. FERRELL
Inventor's signature
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Residence 206 Maple Ave., Pittsburgh, PA 15218
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Post Office Address Same as above

Full name of sole or third inventor Alan SHULDINER
Inventor's signature
Date
Residence 10600 Harpoon Hill, Columbia, MD 21044
Citizenship US
Post Office Address Same as above

Docket No. 108172-00071 ARENT FOX KINTNER PLOTKIN & KAHN, PLLC

Declaration For U.S. Patent Application

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention **entitled**
(Insert Title) GENETIC MARKERS WHICH IDENTIFY INDIVIDUALS WHO IMPROVE THEIR CHOLESTEROL LEVELS AND DIABETES STATUS WITH EXERCISE
the specification of which is attached hereto unless the following box is checked:

☒ was filed on December 8, 1999 As PCT International Application
Number PCT/US99/27919 and was amended on _____
and/or was filed on June 7, 2001 As U.S. Patent Application
Number 09/856,470 and was amended on _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment referred to above.
I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56.
I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate or PCT International Application having a filing date before that of the application(s) for which priority is claimed:

(List prior foreign applications)	(Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed
				☐ Yes ☐ No
				☐ Yes ☐ No
				☐ Yes ☐ No

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

60/111,494 (Application Number)	December 8, 1998 (Filing Date)
60/112,604 (Application Number)	December 17, 1998 (Filing Date)

☐ See attached list for additional prior foreign or provisional applications.

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) or §365(c) of any PCT International application(s) designating the United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) (U.S. or PCT) in the manner provided by the first paragraph of 35, U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(List prior U.S. Applications or PCT International applications designating the U S)	(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

And I hereby appoint the firm of Arent Fox, Customer Number 004372 including as principal attorneys: Robert B. Murray, Reg. No. 22,980; Charles M. Marmelstein, Reg. No. 25,895; George E. Oram, Jr., Reg. No 27,931; Douglas H. Goldhush, Reg. No. 33,125; David T. Nikaido, Reg. No. 22,663; Richard J. Berman, Reg. No. 39,107; King L. Wong, Reg. No. 37,500; James A. Poulos, III, Reg. No. 31,714; Murat Ozgu, Reg. No. 44,275; Robert K. Carpenter, Reg. No. 34,794; Gregory B. Kang, Reg. No. 45,273; Rustan Hill, Reg. No. 37,351; Carl Schaukowitch, Reg. No. 29,211; Kevin Turner, Reg. No. 43,437; Rhonda C. Barton, Reg. No. P47,271; Hans J. Crosby, Reg. No. 44,634, David D. Dzara, Reg. No. 47,543, Lynne D. Anderson, Reg. No. 46,412; David D. Dzara, Reg. No. 47,543; and Laurence J. Edson, Reg. No. 44,666.

Please direct all communications to the following address:

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1050 Connecticut Avenue, N.W., Suite 600
Washington, D.C. 20036-5339
Telephone No. (202) 857-6000; Facsimile No. (202) 638-4810

The undersigned hereby authorizes the U.S. attorneys named herein to accept and follow instructions from the undersigned's assignee, if any, and/or, if the undersigned is not a resident of the United States, the undersigned's domestic attorney, patent attorney or patent agent, as to any action to be take in the Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and the undersigned. In the event of a change in the person(s) from whom instructions may be taken, the U.S. attorneys named herein will be so notified by the undersigned

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor James M. HAGBERG
Inventor's signature ______________________ ______________ Date
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Citizenship US
Post Office Address Same as above

2 Full name of sole or second inventor Robert E. FERRELL
Inventor's signature [signature] 6/20/01 Date
Residence 206 Maple Ave., Pittsburgh, PA 15218 PA
Citizenship US
Post Office Address Same as above

Full name of sole or third inventor Alan SHULDINER
Inventor's signature ______________________ ______________ Date
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Citizenship US
Post Office Address Same as above

Docket No. 108172-00071 ARENT FOX KINTNER PLOTKIN & KAHN, PLLC

Declaration For U.S. Patent Application

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3-00
Full name of sole or third inventor Alan SHULDINER
Inventor's signature [signature] 6/20/01
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